Macular Hole Formation

New Data Provided by Optical Coherence Tomography

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Objective: To establish the sequence of events leading from vitreofoveal traction to full-thickness macular hole formation.

Methods: Both eyes of 76 patients with a full-thickness macular hole in at least 1 eye were examined by biomicroscopy and optical coherence tomography.

Results: Sixty-one fellow eyes had a normal macula. Optical coherence tomograms showed central detachment of the posterior hyaloid over the posterior pole in 19 cases (31%) and a perifoveal hyaloid detachment not detected on biomicroscopy in 26 cases (42%). In the 4 impending macular holes, optical coherence tomography disclosed various degrees of intrafoveal split or cyst, with adherence of the posterior hyaloid to the foveal center and convex perifoveal detachment. In the 14 stage 2 holes, eccentric opening of the roof of the hole was observed, and in the 24 stage 3 holes, the posterior hyaloid was detached from the entire posterior pole.

Conclusions: In fellow eyes of eyes with macular holes posterior hyaloid detachment begins around the macula, but the hyaloid remains adherent to the foveolar center, indicating the action of anteroposterior forces. This results in an intraretinal split evolving into a cystic space, and then to the disruption of the outer retinal layer and the opening of the foveal floor, thus constituting a full-thickness macular hole.


Macular Hole surgery in its current form has a high success rate.1-7 However, although there is general agreement on the need to peel off the posterior hyaloid and to use a long-acting gas as an internal tamponade, the reasons for performing posterior hyaloid ablation are not completely clear. The prevailing view is based on the theory of tangential vitreous traction on the macula proposed by Gass8,9 and Johnson and Gass.10 It is generally assumed that, for stage 2 and 3 holes, hyaloid removal is necessary to relieve the traction of the vitreous on the hole edges. Other hypotheses have also been suggested; in particular, the role of anteroposterior traction exerted by vitreous fibers on the foveolar center.11,12 One of the reasons for these different opinions was the difficulty of establishing the shallow detachment of the posterior hyaloid in front of the macula, even with improved slit-lamp biomicroscopy devices.12,13 The recent availability of optical coherence tomography (OCT) has allowed the recording of hitherto unsuspected data regarding the initial stages of posterior hyaloid detachment from the posterior pole.14

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To improve the understanding of the process of macular hole formation, we used OCT to examine both eyes of patients with a macular hole. Examination of the fellow eye provided new findings about the initial stages of development of idiopathic full-thickness macular holes.

REPORT OF CASES

CASE 1

A 65-year-old woman was examined for a stage 3 full-thickness macular hole in her right eye. Visual acuity was 20/20 OS, no posterior vitreous detachment was found, and the macula was normal on biomi-
PATIENTS AND METHODS

From November 1996 to November 1997, we used OCT to examine both eyes of 76 patients who had a macular hole in at least 1 eye, after obtaining informed consent. Forty-eight patients (63%) were women and the mean age was 65 years. Twenty-two patients had already had 1 eye operated on for a macular hole, so that only 54 eyes had various stages of macular hole at the time of the OCT examination.

CLINICAL EXAMINATION

Standard examination included recording of the onset of symptoms, measurement of visual acuity on Early Treatment of Diabetic Retinopathy Study charts, and fundus examination by biomicroscopy, fundus photography, and fluorescein angiography. Fundus biomicroscopy was performed by 2 retinal specialists (A.G. and P.M.). The fundus was first examined with the Super Pupil (Volk Optical Inc, Mentor, Ohio) noncontact lens, using the angle reducer of the slit-lamp, as this combination provided an excellent depth of field for examination of the vitreous body and assessment of the posterior hyaloid. In addition, the macula was examined with the Centrals direct contact lens (Volk Optical Inc) using the maximum stereoscopy of the slitlamp. The Watzke test was performed with the slit vertical and horizontal. Each macular hole was graded according to the classification proposed by Gass.10 In accordance with this classification, posterior vitreous detachment was only considered to be present if the Weiss ring was seen to be freely detached from the fundus and to move in the plane of the posterior hyaloid, inside the vitreous cavity.

OCT EXAMINATION

We used commercially available OCT equipment derived from the prototype described by Hee et al14 and Puliafito et al.13 The principle of OCT is based on low coherence interferometry. The light source is a superluminescent diode operating at 840 nm that provides a probe beam of low-coherence light on the retina. Cross-sectional tomographic images are constructed by integrating 100 axial measurements in 1 second while scanning the probe beam across the retina. The lateral resolution is limited by the separation between 2 adjacent scans on the retina and varied from 30 µm for the 3-mm scans to 70 µm for the 7-mm scans used in this study. The longitudinal definition ranges between 10 and 13 µm. The images are displayed in false color. Optical coherence tomography images are displayed twice-expanded in the vertical or axial direction.14,15

For each patient, we performed 6 radial scans of 3 mm long, at equally spaced angular orientations centered on the foveola, as well as 3 overlapping 7-mm scans extending from the temporal side of the macula to the nasal side of the optic disc (Figure 1). To detect the faint reflectivity of the posterior hyaloid, the incident light was used at its maximum intensity of 750 µW.

RESULTS

BIOMICROSCOPY FINDINGS

Among the 76 first eyes examined, biomicroscopy diagnosed 14 stage 2 macular holes, 19 stage 3 holes, and 21 stage 4 holes. Twenty-two eyes had already been operated on for a full-thickness hole.

In the fellow eye, biomicroscopy diagnosed 2 stage 1 holes, no stage 2 holes, 5 stage 3 holes, and 4 stage 4 holes. Two cases were considered to be lamellar holes. Posterior vitreous detachment was only seen in 12 cases (4 stage 4 holes, the 2 cases of lamellar holes, and 6 cases with a biomicroscopically normal macula). The distribution of macular hole stages and the presence of an operculum or pseudo-operculum are presented in Table 1. In the 63 fellow eyes with an apparently normal macula, posterior vitreous detachment was only detected by biomicroscopy in 6 cases, and the posterior hyaloid was considered to be still attached to the retina in the 57 other cases. However, OCT examination provided new findings in most of the cases.

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OCT FINDINGS

Normal Macular Contour

Sixty-one of the 63 fellow eyes with a normal macula on fundus biomicroscopy had a normal macular contour and thickness on OCT scans, and 2 had a foveal split or cyst (Table 2). In 6 of these 61 cases the scans showed no preretinal reflectivity over the posterior pole: as posterior vitreous detachment was definitely present on biomicroscopy, the posterior hyaloid was considered detached and out of range of the OCT scanning. In 10 cases, no preretinal reflectivity was detected over the posterior pole on OCT scans; as none of these cases had posterior vitreous detachment on biomicroscopy, the posterior hyaloid was considered still attached.

In the 45 other cases, OCT recorded reflectivity of a preretinal structure that was slightly detached from the posterior pole, remained partially connected to the retina, and had the characteristics of the posterior hyaloid—ie, it was thin, minimally reflective, and continuous.

In 26 of these 45 cases, the posterior hyaloid was detached around the macula but remained attached to the foveal center (Figure 4). This perifoveal detachment extended away from the center in varying degrees (Figure 5). We also observed that, with time, the hyaloid detachment increased in 5 cases, as did the convex elevation of the perifoveal hyaloid (Figure 2, top right and center left).

In the other 19 cases, OCT showed that the posterior hyaloid was detached over the entire posterior pole, from the disc margin to the temporal part of the macula (Figure 6, top). The height of the separation varied from 120 to 600 µm. In 7 of these 19 cases, the posterior hyaloid contained a small prefoveal hyperreflective structure that had not been seen on biomicroscopy (Figure 6, bottom).

Impending Macular Holes

In 4 eyes (all fellow eyes), the foveolar pit was flattened or elevated, and the foveola was thickened by a hyporeflective cystic formation. In 2 of these eyes, which had been considered normal on biomicroscopy and had normal vision, OCT revealed an intraretinal split in the inner part of the foveal center, with adhesion of the partially detached posterior hyaloid suggesting vitreoretinal traction. In the other 2 eyes, which exhibited impending holes on biomicroscopy, OCT disclosed a larger cystic formation disrupting the outer layer of the macula, combined with an elevation of the foveal floor (Figure 7). Its shape was consistent with the possibility of a centrifugal separation of the photoreceptors, rather than with a posterior foveolar detachment of the photoreceptors. The hyaloid remained attached to the center of the foveola.

Full-Thickness Macular Holes

For the 14 stage 2 holes diagnosed with biomicroscopy (all in the first eye), the OCT scans provided very typi-
cal images. The posterior hyaloid was distinctly visible. It adhered to the incompletely detached operculum and was widely separated from the retina around the hole (Figure 3 and Figure 8). The central cyst that characterized the impending hole had left room for a gap between the hole’s edges, which had thickened and contained hyporeflective microcystic spaces. The operculum was incompletely detached and seemed to belong to the retina, as it had the same reflectivity and formed a continuous structure with the inner retina. In the hole’s edges, 2 superimposed retinal structures were still recognizable: the thickened photoreceptor and Henle fiber layers and the inner retinal layers (Figure 9).

In all the 24 stage 3 holes (19 in the first eye and 5 in the fellow eye) the edges of the hole had thickened and contained variously large, hyporeflective cystic spaces in both the inner and outer retina. The elevation of the hole edge was more due to this thickening than to the detachment of the edge (Figure 10). In no case did we observe what has been termed vitreofoveal separation; ie, a local separation of the hyaloid from the hole edge, with persistence of vitreoretinal adherence around the hole.9,10 On 7-mm OCT scans, the posterior hyaloid seemed to be completely separated from the retina over the entire surface of the posterior pole, except at the optic disc, and contained a hyperreflective structure resembling an operculum, which in 4 eyes had not been detected by biomicroscopy. The distance between the hyaloid and the retinal surface varied from 200 to 500 µm.

**COMMENT**

Many hypotheses have been formulated regarding the mechanisms of macular hole formation. In 1983, Avila et al11 suspected intravitreous anteroposterior traction to be the cause of macular holes, thus confirming previous reports.16 This concept was replaced in the late 1980s by the Gass hypothesis that the holes were due to tangential traction of the vitreous cortex at the foveolar edges, and the operculum was no longer considered to constitute the full thickness of the foveolar neural tissue. This might explain the surprisingly good visual recovery after successful macular hole surgery.9 However, several observers continued to report new findings in favor of anteroposterior traction. Akiba et al17 assumed that anteriorly oriented vector forces to the macula might contribute to the development of macular holes. Kakekashi et al12 produced new biomicroscopic evidence for an-
teroposterior traction on the operculum of macular holes. However, they postulated that this traction was due to direct attachment of vitreous fibers to the foveola rather than to partial detachment of the posterior hyaloid. Kim et al,18 who studied the natural history of stage 2 macular holes, also concluded that some component of obliquely oriented anteroposterior vitreous traction may be important in the pathogenesis of macular holes.

Other hypotheses involved the formation of an intraretinal cyst as the prime mover of hole formation, due either to a tractional19 or a degenerative process.20,21

One of the major difficulties in establishing what happens during macular hole formation is the poor visibility of the posterior hyaloid when it is only slightly separated from the retina, and the lack of definition of the optic cross section of the macula provided by slitlamp examination. Despite the excellent observations made in some cases thanks to a slitlamp photography device, the slightly detached posterior hyaloid was rarely visible.11,12,17,22 Other observations made with a scanning laser ophthalmoscope indirectly supported the hypothesis that a central foveal cyst constitutes the first event in macular hole development.23

These observations were also supported by laser slitlamp photographs, showing that macular holes develop together with intraretinal cystic changes.13

Finally, OCT recently provided new and unexpected information about vitreoretinal relationships, and also about the intraretinal changes that occur at the macular center during the initial stages of macular hole formation.15 Hee et al14 have already shown that OCT was able to detect small perifoveal detachment of the posterior hyaloid, minimally reflective spaces within the fovea in stage 1 holes, and vitreofoveal traction resulting in foveal cyst formation. The good correlation between macular OCT images and histological macular structure was recently highlighted by an experimental clinicanoanatomical comparison.24 In clinical practice, commercially available OCT equipment at least allows the layer of photoreceptors and Henle fibers to be distinguished.
from the inner retina. Moreover, when the detached posterior vitreous cortex remains close to the retina, it is easily detected as a continuous minimally reflective structure.\textsuperscript{14,15} Van Newkirk et al\textsuperscript{25} were also able to detect, by ultrasonography, a thin membranous preretinal interface attached to a pseudo-operculum and forming a cord over the curvature of the macular area. They proposed several explanations for this image, including partial posterior hyaloid detachment and the reflection of the anterior surface of the thick cortical vitreous. We have been using OCT, particularly for the fellow eye of macular holes, to detect the initial stages of vitreous separation and foveal alteration. Our most common finding was that posterior hyaloid detachment began at the posterior pole, around the macula. The idea that posterior vitreous detachment begins at the posterior pole had been postulated on the basis of anatomical findings\textsuperscript{26} and biomicroscopic observations.\textsuperscript{11} It was also thought that the foveola was one of the preferential zones of vitreoretinal adherence\textsuperscript{16,27-31} though it was not proven. However, the progression of the initial stages of posterior hyaloid detachment has never been shown as we were able to show it by OCT examination in 5 cases, in which we observed that it began at the periphery of the macula, usually on its nasal side, and then gradually spread around the entire macula while the hyaloid remained focally adherent to the foveal center. As the posterior hyaloid remained attached to the center of the foveola and to the optic disc, it displayed a convexity that may indicate the exertion of anteroposterior traction on its vitreous side.

The mechanism resulting in posterior vitreous detachment is poorly understood. According to some authors, it involves the occurrence of a hole in the premacular hyaloid through which anteroposterior collagen fibers could be directly inserted into the foveal pit.\textsuperscript{27-32} Other authors described a “premacular bursa” that does not support the possibility of anteroposterior traction.\textsuperscript{33,34} Optical coherence tomographic examination makes it clear that the posterior vitreous cortex constitutes a continuous sheet with characteristic backscattering, which fits well with the

\textbf{Figure 10.} Stage 3 hole. Top, Optical coherence tomogram (3 mm long) shows the hyperreflective operculum (arrow) next to the minimally reflective membrane corresponding to the posterior hyaloid. The edges of the hole are thickened by cystic spaces and detached from the retinal pigment epithelium by \textasciitilde{}50 \(\mu\)m (arrowheads). Bottom, Composite optical coherence tomogram shows the detachment of the posterior hyaloid from the entire posterior hole. OD indicates optic disc.

\textbf{Figure 11.} Section through the center of the fovea. ON indicates the outer nuclear layer; OH, outer layer of Henle fibers; and INL, the inner nuclear layer. In the 200 \(\mu\)m of the central area of the fovea, the outer cone fibers are separated from each other by the processes of the radial fibers of Müller. The inner processes of the Müller cells occupy most of the inner third of the retinal thickness, thus constituting the floor of the center of the foveola (reprinted with permission from Arch Ophthalmol\textsuperscript{35}).
either as an involutional process or as a form of genesis was controversial, and has been interpreted widely accepted in the past, even though its pathogenesis was controversial, and has been interpreted either as an involutional process or as a form of mechanical traction.

We showed that the first stage of macular hole formation was an intraretinal split in the inner part of the foveola, which evolved into a cystic formation. Once this formation has extended posteriorly, disrupting the photoreceptor layer, and vitreous traction has resulted in the opening of the roof of the cyst, a full-thickness macular hole occurs. The occurrence of a foveolar cyst as the first stage in macular hole formation has been widely accepted in the past, even though its pathogenesis was controversial, and has been interpreted either as an involutional process or as a form of mechanical traction.

On the other hand, Gass proposed that the initial appearance of impending holes was caused instead by posterior foveolar detachment. On the basis of scanning laser ophthalmoscope findings, Kishi et al concluded that intraretinal splitting or cyst formation caused by tractional elevation of the Henle fiber layer was the initial feature of macular hole development. Asrani et al, using OCT examination, provided images of these cystic changes in the macula and showed that they were related to the posterior hyaloid attachment to the foveolar center. One cannot exclude the possible presence of artifacts, especially because the hyporeflective intrafoveal spaces could be due to a change in the arrangement of retinal elements rather than to cystic spaces. Nevertheless, many arguments support the latter hypothesis.

The location of the intraretinal split in the inner foveola may be explained by its particular ultrastructure, which in humans was analyzed in particular by Yamada in 1969 and Hogan et al in 1971. It appears that a cleavage plane exists in the inner part of the foveola. Muller cell processes occupy most of the inner third of the foveolar center, thus constituting the floor of this center (Figure 11). The intrafoveal split due to the exertion of anteroposterior traction of the vitreous probably occurs at this level, causing various degrees of damage to the very central Muller cell processes. Centrally, the disorganization of the glial structure of the foveola might result in a cystic space, and laterally in the splitting of bipolar and ganglion cells away from the Henle fiber layer. At this stage of the impending hole, the OCT image is composed of an inner hyperreflective structure (the roof of the cyst), a hyporeflective space that corresponds to the split or cyst, and an outer hyperreflective structure that may correspond to the thickened photoreceptors and Henle fibers. Even before the opening of the operculum, the central photoreceptors tend to open, leaving a hyporeflective space in the center. The operculum might result from a lamellar avulsion of the foveal floor containing vitreous collagen, Muller cell elements, and, occasionally, inner portion of cones torn away with the Muller cells. In all our cases of stage 2 holes, the operculum had the same reflectivity as the adjacent inner retina.

In stage 3 holes we never saw any connection between the hole’s edges and the posterior hyaloid, which was completely detached over all the posterior pole except at the optic disc. A variously reflective operculum was seen in all cases. The hole’s edges were thickened by intraretinal cystic cavities.

In conclusion, we showed that, in fellow eyes of macular holes, posterior hyaloid detachment begins around the macula. The convex shape of this detachment might indicate the action of anteroposterior forces, which might exert traction on the foveolar center. The first change observed in the macular tissue is an intraretinal split evolving into a cystic space: this constitutes the stage 1 or impending macular hole. The posterior expansion of the cyst and the eccentric opening of its roof, due to the vitreous traction, constitutes stage 2. In stage 3 holes, the posterior hyaloid is completely detached from the macula, and contains the operculum (Figure 12).
Errors in Case Report. In the article titled “Increased Iris Pigment in a Child Due to Late-onset Proxst,” in the December issue of the ARCHIVES (Arch Ophthalmol. 1998;116:1683-1684), 3 errors occurred. First, the last sentence of paragraph 3 should have read “A diagnosis of glaucoma was not made, although a documented myopic shift from –3.5 diopters (D) to –5.5 D OD occurred within 1 month (+0.75 D OS).” Second, in the first column on page 1684, the sentence that begins on line 23 should have read “latanoprost successfully lowered intraocular pressure to 17 to 22 mm Hg.” Finally, the parenthetical comment on line 8 of the first full paragraph in the second column on page 1684 should have read “(mean, 4.5 months).” The journal regrets these errors.